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Signed Stephen Hordley

Dated 27 August 2004

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1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — 101243

160CT03 E845023-1 D02934
P01/7700 0.00-0324236.9

2. Patent application number *(The Patent Office will fill in this part)* — 0324236.9

16 OCT 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
SE-151 85 Sodertalje
Sweden

Patents ADP number *(if you know it)* 78224480003

If the applicant is a corporate body, give the country/state of its incorporation — Sweden

4. Title of the invention — CHEMICAL COMPOUNDS

5. Name of your agent *(if you have one)* — Kevin Bill

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca
Global Intellectual Property
PO Box 272
Mereside, Alderley Park
Macclesfield, Cheshire SK10 4TG

Patents ADP number *(if you know it)* 44698470004

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	40
Claim(s)	03
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Authorised Signatory Date 15/10/2003

12. Name and daytime telephone number of person to contact in the United Kingdom: Helen Dixon - 01625 517301

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Notes

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CHEMICAL COMPOUNDS

The present invention relates to compounds which inhibit dipeptidyl peptidase IV (DPP-IV) activity, processes for their preparation, pharmaceutical compositions containing them as the active ingredient, methods for the treatment of disease states associated with DPP-IV activity, to their use as medicaments and to their use in the manufacture of medicaments for use in the inhibition of DPP-IV in warm-blooded animals such as humans. In particular this invention relates to compounds useful for the treatment of diabetes mellitus in warm-blooded animals such as humans, more particularly to the use of these compounds in the manufacture of medicaments for use in the treatment of diabetes mellitus in warm-blooded animals such as humans.

DPP-IV is a serine protease found throughout the body, which degrades and regulates the activity of several regulatory peptides in man including glucagon-like peptide-1 (GLP-1), GLP-2, GHRH (growth hormone releasing hormone) and GIP (glucagon interacting peptide). GLP-1 is a peptide hormone which is released from the intestinal tract wall into the bloodstream in response to a meal and strongly influences post-prandial glucose metabolism. As post-prandial glucose levels rise, GLP-1 acts directly on pancreatic β-cells to augment insulin release and also promote new insulin biosynthesis. Simultaneously, GLP-1 delays gastric emptying, further suppressing meal-related rise in plasma glucose. It has been shown (Rachman, J. et al, (1997), *Diabetologia*, **40**, 205-211; Nauck, M.A. et al, (1996), *Diabetologia*, **39**, 1546-1553; Gutniak, M.K. et al, (1994), *Diabetes Care*, **17**, 1039-1045; Rachman J. et al, (1996) *Diabetes*, **45**, 1524-1530) that GLP-1 administration either subcutaneously or by intravenous infusion improves glucose tolerance in diabetic patients, however daily administration of GLP-1 is not generally considered to be a desirable form of therapy.

DPP-IV degrades GLP-1 circulating in the bloodstream and inhibition of DPP-IV activity causes an increase in the half life, and therefore activity, of GLP-1. Additionally DPP-IV inhibitors have beneficial effects on pancreatic failure: Ribel U. et al ((2001) Diabetologia, 44, A192, 738) described how the DPP-IV inhibitor valine pyrrolidide (VP) promoted differentiation of new beta cells in 60% pancreatectomised rats. Therefore, administration of a DPP-IV inhibitor should result in prolongation of endogenous GLP-1 activity and thus potentially in a clinically significant lowering of diabetic hyperglycemia. A DPP-IV inhibitor may potentially be useful for the prevention, delay or treatment of Type 2 (non-insulin

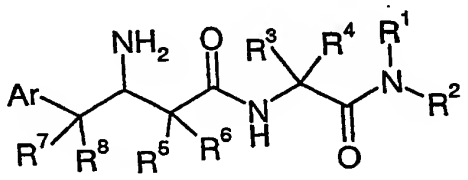
dependent) diabetes mellitus.

Novel DPP-IV inhibitors have been described in the art. Many are 2-cyanopyrrolidines derivatives with a significant range of substituents bonded to the ring nitrogen (see for example WO 98/19998, WO 00/34241, WO 01/96295, WO 01/40180), or contain this structure (see for example WO 00/168603 which discloses cyclopropyl fused cyano pyrrolidines). Others are cyanothiazolidines (see for example US 00/6110949, US 00/6107317, WO 99/61431), also with a variety of substituents bonded to the ring nitrogen. Still others contain pyrrolidine, piperidine, or morpholine rings which may contain substituents on the ring carbon atoms other than cyano groups (see for example WO 03/000181 and WO 03/000180).

We have surprisingly found a new structural class of DPP-IV inhibitors.

Accordingly, the present invention provides a compound of formula (I)

or a pharmaceutically-acceptable salt thereof,



(I)

wherein:

Ar is phenyl optionally substituted with 1, 2, 3, 4 or 5 groups independently selected from R^9;

R^9 is selected from halo, (1-6C)alkyl (optionally substituted with 1-5 halo), (1-6C)alkoxy (optionally substituted with 1-5 halo) and cyano;

R^1 is selected from hydrogen and (1-6C)alkyl;

R^2 is selected from hydrogen, (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylAR2, -(1-6C)alkyl(3-8C)cycloalkyl, -(1-6C)alkylHET1, -(1-6C)alkylHET2, -(1-6C)alkylCO_2(1-6C)alkyl, -(1-6C)alkylCO_2(3-8C)cycloalkyl, -(1-6C)alkylCO_2AR1, -(1-6C)alkylCO_2HET1, -(1-6C)alkylOCO(1-6C)alkyl, -(1-6C)alkylOCO(3-8C)cycloalkyl, -(1-6C)alkylOCOAR1, -(1-6C)alkylOCOHET1, -(1-6C)alkylCO(1-6C)alkyl, -(1-6C)alkylCO(3-8C)cycloalkyl, -(1-6C)alkylCOAR1, -(1-6C)alkylCOHET1, -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCO(3-8C)cycloalkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONH(3-8C)cycloalkyl,

-(1-6C)alkylCON-di(1-6C)alkyl, -(1-6C)alkylCONHAR1,
-(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylN-di(1-6C)alkyl , -(1-6C)alkylNHAR1,
-(1-6C)alkylNH(HET1), -(1-6C)alkylNHSO$_2$(1-6C)alkyl, -(1-6C)alkylSO$_2$NH(1-6C)alkyl,
and -(1-6C)alkylSO$_2$N-di(1-6C)alkyl;

or

R^1 and R^2 may together form a (3-8C)cycloalkyl , (5-12C)bicycloalkyl, or (6-12C)tricycloalkyl ring, or a ring defined by HET1; wherein a ring comprising R^1 and R^2 is optionally substituted by 1 or 2 substituents independently selected from halo, (1-6C)alkyl, halo(1-6C)alkyl, (1-6C)alkoxy, cyano, carboxy, carboxy(1-6C)alkyl, –CO(1-6C)alkyl, –CO$_2$(1-6C)alkyl, (1-6C)alkylamino, di-(1-6C)alkylamino, –NHCO(1-6C)alkyl, –CONH(1-6C)alkyl, -CONdi-(1-6C)alkyl and HET1;

R^3 and R^4 are independently selected from hydrogen, (1-6C)alkyl, -(1-6C)alkyl(3-8C)cycloalkyl, -(1-6C)alkyl(3-8C)cycloalkenyl, -(1-6C)alkylAR1, -(1-6C)alkylAR2, -(1-6C)alkylHET1, and -(1-6C)alkylHET2; or

R^3 and R^4 together form a ring as defined by (3-8C)cycloalkyl, AR2, HET1 or HET2;

R^5, R^6, R^7 and R^8 are independently selected from hydrogen and (1-6C)alkyl;

AR1 is optionally substituted phenyl;

AR2 is an optionally substituted 8-, 9- or 10-membered, unsaturated, partially or fully saturated bicyclic carbocylic ring;

HET1 is an optionally substituted 3-, 4-, 5- or 6-membered, unsaturated, partially or fully saturated monocyclic heterocyclyl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), linked via a ring carbon atom, or a ring nitrogen atom if the ring is not thereby quaternised, and wherein any available carbon, sulfur or nitrogen atom may be oxidised;

HET2 is an optionally substituted 8-, 9- or 10-membered, unsaturated, partially or fully saturated bicyclic heterocyclyl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and linked via a ring carbon atom in either of the rings comprising the bicyclic system;

wherein suitable optional substituents on AR1, AR2, HET1 and HET2 are 1, 2, 3, 4 or 5 substituents independently selected from halo, (1-6C)alkyl, halo(1-6C)alkyl, dihalo(1-6C)alkyl, trifluoromethyl, (1-6C)alkoxy, carboxy(1-6C)alkyl, carboxy(1-6C)alkoxy, hydroxy, amino, (1-6C)alkylamino, di(1-6C)alkylamino, -CONH$_2$, –CONH(1-6C)alkyl, -CONdi(1-6C)alkyl, –NHCO(1-6C)alkyl, -S(O)$_2$NH$_2$, –SO$_2$NH(1-6C)alkyl, -SO$_2$Ndi(1-

6C)alkyl and –$NHSO_2$(1-6C)alkyl.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined' or 'defined hereinbefore' the said group encompasses the first occurring and broadest definition as well as each and all of the particular definitions for that group.

It is to be understood that where substituents contain two substituents on an alkyl chain, in which both are linked by a heteroatom (for example two alkoxy substituents), then these two substituents are not substituents on the same carbon atom of the alkyl chain.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. An analogous convention applies to other generic terms. Unless otherwise stated the term "alkyl" advantageously refers to chains with 1-6 carbon atoms, preferably 1-4 carbon atoms.

In this specification the term "alkoxy" means an alkyl group as defined hereinbefore linked to an oxygen atom.

It is to be understood that optional substituents on any group may be attached to any available atom as appropriate unless otherwise specified, including heteroatoms provided that they are not thereby quaternised.

Within this specification composite terms are used to describe groups comprising more that one functionality such as –(1-6C)alkylNHSO_2(1-6C)alkyl. Such terms are to be interpreted in accordance with the meaning which is understood by a person skilled in the art for each component part. For example –(1-46)alkylNHSO_2(1-6C)alkyl includes –methylaminosulphonylmethyl, -methylaminosulphonylethyl, -ethylaminosulphonylmethyl, and -propylaminosulphonylbutyl.

Where optional substituents are chosen from "0, 1, 2 or 3" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups. An analogous convention applies to substituents chose from "0, 1 or 2" groups and "1 or 2" groups.

Substituents may be present at any suitable position on, for example, an alkyl group. Therefore, hydroxy substituted (1-6C)alkyl includes hydroxymethyl, 1-hydroxyethyl,

2-hydroxyethyl and 3-hydroxypropyl.

Examples of **(1-4C)alkyl** include methyl, ethyl, propyl and isopropyl; examples of **(1-6C)alkyl** include methyl, ethyl, propyl, isopropyl, t-butyl, pentyl, iso-pentyl, 1-2-dimethylpropyl and hexyl; examples of **(3-8C)cycloalkyl** include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; examples of **(3-8C)cycloalkenyl** include cyclopropenyl, cyclobutenyl, cyclopentenyl and cyclohexenyl; examples of **(5-12C)bicycloalkyl** include norbornyl, decalinyl (bicyclo[4,4,0]decyl (cis and trans), bicyclo[5,3,0]decyl and hydrindanyl (bicyclo[4,3,0]nonyl); examples of **(6-12)tricycloalkyl** include adamantyl (tricyclo[3,3,1,1]decyl), homoadamantyl (tricyclo[4,3,1,1]undecyl) and isomers of perhydrophenanthrene; examples of **–(1-6C)alkyl(3-8C)cycloalkyl** include –(1-4C)alkyl(3-6C)cycloalky;, such as cyclopropylmethyl, cyclopropylethyl, cyclopropylpropyl, cyclopropylbutyl, cyclobutylmethyl, cyclopentylethyl, cyclohexylmethyl, cyclohexylpropyl and cyclohexylbutyl; examples of **–(1-6C)alkyl(3-8C)cycloalkenyl** include –(1-4C)alkyl(3-6C)cycloalkenyl, such as cyclopropenylmethyl, cyclopropenylethyl, cyclopropenylpropyl, cyclopropenylbutyl, cyclobutenylmethyl, cyclopentenylethyl, cyclohexenylmethyl and cyclohexadienylmethyl; examples of **(1-6C)alkoxy** include methoxy, ethoxy, propoxy, isopropoxy, tert-butoxy and pentoxy; examples of **halo** are chloro, bromo, fluoro and iodo; examples of **halo(1-6C)alkyl** include chloromethyl, fluoroethyl and fluoromethyl; examples of **dihalo(1-6C)alkyl** include dichloromethyl, difluoromethyl, 1,2-difluoroethyl and 1,1-difluoroethyl; examples of **hydroxy(1-6C)alkyl** include hydroxy methyl, 1-hydroxyethyl, 2-hydroxyethyl and 3-hydroxybutyl; examples of **carboxy(1-6C)alkyl** include carboxymethyl, 1-carboxyethyl, 2-carboxyethyl, 2-carboxypropyl and 3-carboxypropyl; examples of **carboxy(1-6C)alkoxy** include carboxymethoxy, 1-carboxyethoxy, 2-carboxyethoxy, 2-carboxypropoxy and 3-carboxypropoxyl; examples of **(1-6C)alkylamino** include methylamino, ethylamino and propylamino; examples of **di-((1-6C)alkyl)amino** include dimethylamino, N-ethyl-N-methylamino, diethylamino, N-methyl-N-propylamino and di-isopropylamino; examples of **–CO(1-6C)alkyl** include –CO(1-4C)alkyl such as methylcarbonyl, ethylcarbonyl, propylcarbonyl, iso-propylcarbonyl and tert-butylcarbonyl; examples of **–CO_2(1-6C)alkyl** include –CO_2(1-4C)alkyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, iso-propoxycarbonyl and tert-butoxycarbonyl; examples of **–NHCO(1-6C)alkyl** include –NHCO(1-4C)alkyl such as methylcarbonylamino, ethylcarbonylamino, propylcarbonylamino, iso-propylcarbonylamino and tert-

butylcarbonylamino; examples of **–CONH(1-6C)alkyl** include –CONH(1-4C)alkyl such as methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, iso-propylaminocarbonyl and tert-butylaminocarbonyl; examples of **–CONdi(1-6C)alkyl** include –CONdi(1-4C)alkyl such as dimethylaminocarbonyl, N-methyl-N-ethylaminocarbonyl, diethylaminocarbonyl, N-methyl-N-propylaminocarbonyl and di-isopropylaminocarbonyl; examples of **–SO_2NH(1-6C)alkyl** include –SO_2NH(1-4C)alkyl such as methylaminosulfonyl, ethylaminosulfonyl, propylaminosulfonyl, iso-propylaminosulfonyl and tert-butylaminosulfonyl; examples of **–SO_2Ndi(1-6C)alkyl** include –SO_2Ndi(1-4C)alkyl such as dimethylaminosulfonyl, N-methyl-N-ethylaminosulfonyl, diethylaminosulfonyl, N-methyl-N-propylaminosulfonyl and di-isopropylaminosulfonyl; examples of **–NHSO_2(1-6C)alkyl** include –NHSO_2(1-4C)alkyl such as methylsulfonylamino, ethylsulfonylamino, propylsulfonylamino, iso-propylsulfonylamino and tert-butylsulfonylamino;

examples of **–(1-6C)alkylCO(1-6C)alkyl** include –(1-4C)alkylCO(1-4C)alkyl such as methylcarbonylmethyl, methylcarbonylbutyl, ethylcarbonymethyl, propylcarbonylbutyl, iso-propylcarbonylmethyl and tert-butylcarbonylmethyl; examples of **–(1-6C)alkylCO(3-8C)alkyl** include –(1-4C)alkylCO(3-6C)alkyl such as cyclopropylcarbonylmethyl, cyclopropylcarbonylbutyl, cyclobutylcarbonymethyl, cyclopentylcarbonylbutyl, cyclohexylcarbonylmethyl and cyclohexylcarbonylmethyl; examples of **–(1-6C)alkylOCO(1-6C)alkyl** include –(1-4C)alkylOCO(1-4C)alkyl such as methylcarbonyloxymethyl, methylcarbonyloxybutyl, ethylcarbonyloxymethyl, propylcarbonyloxybutyl, iso-propylcarbonyloxymethyl and tert-butylcarbonyloxymethyl; examples of **–(1-6C)alkylOCO(3-8C)cycloalkyl** include –(1-4C)alkylOCO(3-6C)alkyl such as cyclopropylcarbonyloxymethyl, cyclopropylcarbonyloxybutyl, cyclobutylcarbonyloxymethyl, cyclopentylcarbonyloxybutyl, cyclohexylcarbonyloxymethyl and cyclohexylcarbonyloxymethyl; examples of **–(1-6C)alkylCO_2(1-6C)alkyl** include –(1-4C)alkylCO_2(1-4C)alkyl such as methoxycarbonylmethyl, methyoxycarbonylbutyl, ethoxycarbonylmethyl, propoxycarbonylmethyl, iso-propoxycarbonylmethyl and tert-butoxycarbonylmethyl; examples of **–(1-6C)alkylCO_2(3-8C)cycloalkyl** include –(1-4C)alkylCO_2(3-6C)cycloalkyl such as cyclopropyloxycarbonylmethyl, cyclopropyloxycarbonylbutyl, cyclobutyloxycarbonylmethyl, cyclopentyloxycarbonylmethyl, cyclohexyloxycarbonylmethyl and cyclohexy;oxycarbonylmethyl; examples of **–(1-6C)alkylNHCO(1-6C)alkyl** include –(1-4C)alkylNHCO(1-4C)alkyl such as methylcarbonylaminomethyl, methylcarbonylaminopropyl, ethylcarbonylaminomethyl,

propylcarbonylaminomethyl, iso-propylcarbonylaminomethyl and tert-butylcarbonylaminomethyl; examples of **–(1-6C)alkylNHCO(3-8C)cycloalkyl** include –(1-4C)alkylNHCO(3-6C)alkyl such as cyclopropylcarbonylaminomethyl, cyclopropylcarbonylaminopropyl, cyclobutylcarbonylaminomethyl, cyclopentylcarbonylaminomethyl, cyclohexylcarbonylaminomethyl and cyclohexylcarbonylaminoethyl; examples of **–(1-6C)alkylCONH(1-6C)alkyl** include –(1-4C)alkylCONH(1-4C)alkyl such as methylaminocarbonylmethyl, methylaminocarbonylpropyl, ethylaminocarbonylmethyl, propylaminocarbonylmethyl, iso-propylaminocarbonylmethyl and tert-butylaminocarbonylmethyl; examples of **–(1-6C)alkylCONdi(1-6C)alkyl** include –(1-4C)alkylCONdi(1-4C)alkyl such as dimethylaminocarbonylmethyl, dimethylaminocarbonylpropyl, N-methyl-N-ethylaminocarbonylmethyl, diethylaminocarbonylmethyl, N-methyl-N-propylaminocarbonylmethyl and di-isopropylaminocarbonylmethyl; examples of **–(1-6C)alkylCONH(3-8C)cycloalkyl** include –(1-4C)alkylCONH(3-6C)alkyl such as cyclopropylaminocarbonylmethyl, cyclopropylaminocarbonylpropyl, cyclobutylaminocarbonylmethyl, cyclopentylaminocarbonylmethyl, cyclohexylaminocarbonylmethyl and cyclohexylaminocarbonylethyl; examples of **–(1-6C)alkylNH(1-6C)alkyl** include –(1-4C)alkylNH(1-4C)alkyl such as methylaminomethyl, methylaminopropyl, ethylaminomethyl, propylaminomethyl, iso-propylaminomethyl and tert-butylaminomethyl; examples of **–(1-6C)alkylNdi(1-6C)alkyl** include –(1-4C)alkylNdi(1-4C)alkyl such as dimethylaminomethyl, dimethylaminopropyl, N-methyl-N-ethylaminomethyl, diethylaminomethyl, N-methyl-N-propylaminomethyl and di-isopropylaminomethyl; examples of **–(1-6C)alkylSO$_2$NH(1-6C)alkyl** include –(1-4C)alkylSO$_2$NH(1-4C)alkyl such as methylaminosulfonylmethyl, methylaminosulfonylpropyl, ethylaminosulfonylmethyl, propylaminosulfonylmethyl, iso-propylaminosulfonylmethyl and tert-butylaminosulfonylmethyl; examples of **–(1-6C)alkylSO$_2$Ndi(1-6C)alkyl** include –(1-4C)alkylSO$_2$Ndi(1-4C)alkyl such as dimethylaminosulfonylmethyl, dimethylaminosulfonylpropyl, N-methyl-N-ethylaminosulfonylmethyl, diethylaminosulfonylmethyl, N-methyl-N-propylaminosulfonylmethyl and di-isopropylaminosulfonylmethyl; examples of **–(1-6C)alkylNHSO$_2$(1-6C)alkyl** include –(1-4C)alkylNHSO$_2$(1-4C)alkyl such as methylsulfonylaminomethyl, methylsulfonylaminopropyl, ethylsulfonylaminomethyl,

propylsulfonylaminomethyl, iso-propylsulfonylaminomethyl and tert-butylsulfonylaminomethyl;

Examples of **–(1-6C)alkylAR1** include (each example being optionally substituted) benzyl, phenylethyl and phenylbutyl. Examples of **–(1-6C)alkylCOAR1** include (each example being optionally substituted) phenylcarbonylmethyl, phenylcarbonylethyl, phenylcarbonylpropyl and phenylcarbonylbutyl. Examples of **–(1-6C)alkylCO$_2$AR1** include (each example being optionally substituted) phenoxycarbonylmethyl, phenoxycarbonylethyl, phenoxycarbonylpropyl and phenoxycarbonylbutyl. Examples of **–(1-6C)alkylOCOAR1** include (each example being optionally substituted) phenylcarbonyloxymethyl, phenylcarbonyloxyethyl, phenylcarbonyloxypropyl and phenylcarbonyloxybutyl. Examples of **–(1-6C)alkylNHCOAR1** include (each example being optionally substituted) phenylcarbonylaminomethyl, phenylcarbonylaminoethyl, phenylcarbonylaminopropyl and phenylcarbonylaminobutyl. Examples of **–(1-6C)alkylCONHAR1** include (each example being optionally substituted) phenylaminocarbonylmethyl, phenylaminocarbonylethyl, phenylaminocarbonylpropyl and phenylaminocarbonylbutyl. Examples of **–(1-6C)alkylNHAR1** include (each example being optionally substituted) phenylaminomethyl, phenylaminoethyl, phenylaminopropyl and phenylaminobutyl.

Particular values for **AR2** include, for example, indanyl, indenyl, dihydronaphthyl and 1,2,3,4-tetrahydronaphthyl.

Examples of **–(1-6C)alkylAR2** include (each example being optionally substituted) indanylmethyl, indanylethyl, indanylpropyl, indanylbutyl, indenylmethyl, indenylethyl, dihydronaphthylmethyl, dihydronaphthylpropyl and 1,2,3,4-tetrahydronaphthylmethyl.

Particular values for **HET1** include, for example (each example being optionally substituted) furyl, pyrrolyl, thiophenyl, pyrazolyl, imidazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, 1,2,3- & 1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxazinyl, oxadiazolyl, thiazolyl, isothiazolyl, 1,2,4- and 1,3,4-thiadiazolyl, oxazoline, thiazoline, dihydropyrrolyl (especially 2,5-dihydropyrrol-4-yl), tetrahydropyridyl (especially 1,2,5,6-tetrahydropyrid-4-yl), tetrahydrofuranyl, , tetrahydrothienyl, 1-oxotetrahydrothienyl, 1,1-dioxotetrahydrothienyl, pyrrolidinyl, oxazolidine, thiazolidine, morpholinyl, thiomorpholinyl, piperazinyl, imidazolyl, piperidyl, 1,3-dioxolan-4-yl, 1,3-dioxan-4-yl, 1,3-dioxan-5-yl and 1,4-dioxan-2-yl.

Further particular values for HET1 include (each value being optionally substituted) furyl, pyrrolyl, thiophenyl, pyrazolyl, imidazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl,

1,2,3- & 1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxazinyl, oxadiazolyl, thiazolyl, isothiazolyl, 1,2,4- and 1,3,4-thiadiazolyl, oxazoline, thiazoline, piperazinyl, imidazolyl.

Further particular values for HET1 include (each value being optionally substituted) dihydropyrrolyl (especially 2,5-dihydropyrrol-4-yl), tetrahydropyridyl (especially 1,2,5,6-tetrahydropyrid-4-yl), tetrahydrofuranyl, tetrahydrothienyl, 1-oxotetrahydrothienyl, 1,1-dioxotetrahydrothienyl, pyrrolidinyl, oxazolidine, thiazolidine, morpholinyl, thiomorpholinyl, piperidyl, 1,3-dioxolan-4-yl, 1,3-dioxan-4-yl, 1,3-dioxan-5-yl and 1,4-dioxan-2-yl.

Examples of **–(1-6C)alkylHET1** include any one of the above particular values for HET1 attached to any value of (1-6C)alkyl, and thus includes for example (optionally substituted) pyridylmethyl, pyridylethyl, pyridylpropyl, pyridylbutyl and pyridylhexyl.

Examples of **–(1-6C)alkylCOHET1** include any one of the above particular values for HET1 attached through a carbonyl group to any value of (1-6C)alkyl, and thus includes for example (optionally substituted) pyridylcarbonylmethyl, pyridylcarbonylethyl, pyridylcarbonylpropyl, pyridylcarbonylbutyl and pyridylcarbonylhexyl.

Examples of **–(1-6C)alkylCO$_2$HET1** include any one of the above particular values for HET1 attached through an oxycarbonyl group to any value of (1-6C)alkyl, and thus includes for example (optionally substituted) pyridyloxycarbonylmethyl, pyridyloxycarbonylethyl, pyridyloxycarbonylpropyl, pyridyloxycarbonylbutyl and pyridyloxycarbonylhexyl.

Examples of **–(1-6C)alkylOCOHET1** include any one of the above particular values for HET1 attached through an carboxy group to any value of (1-6C)alkyl, and thus includes for example (optionally substituted) pyridylcarboxymethyl, pyridylcarboxyethyl, pyridylcarboxypropyl, pyridylcarboxybutyl and pyridylcarboxyhexyl.

Examples of **–(1-6C)alkylNH(HET1)** include any one of the above particular values for HET1 attached through an amino group to any value of (1-6C)alkyl, and thus includes for example (optionally substituted) pyridylaminomethyl, pyridylaminoethyl, pyridylaminopropyl, pyridylaminobutyl and pyridylaminohexyl.

Particular values for **HET2** include for example indole, benzofuranyl, benzothiophenyl, benzimidazolyl, benzothiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, quinolinyl, quinoxalinyl, quinazolinyl, phthalazinyl, cinnolinyl, indolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydrobenzofuranyl, chromanyl, isochromanyl, 2,3-dihydrobenzthiazolyl, 2,3-dihydrobenzimidazolyl, benzodioxolanyl, purinyl and naphthyridinyl.

Further particular examples of HET2 include bicyclic heteroaryl ring systems with at least one bridgehead nitrogen and optionally a further 1-3 heteroatoms chosen from oxygen, sulfur and nitrogen. Specific examples of such ring systems include, for example, 3H-pyrrolo[1,2-a]pyrrolyl, pyrrolo[2,1-b]thiazolyl, 1H-imidazo[1,2-a]pyrrolyl, 1H-imidazo[1,2-a]imidazolyl, 1H,3H-pyrrolo[1,2-c]oxazolyl, 1H-imidazo[1,5-a]pyrrolyl, pyrrolo[1,2-b]isoxazolyl, imidazo[5,1-b]thiazolyl, imidazo[2,1-b]thiazolyl, indolizinyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, pyrazolo[1,5-a]pyridyl, pyrrolo[1,2-b]pyridazinyl, pyrrolo[1,2-c]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-a]pyrimidinyl, pyrido[2,1-c]-s-triazolyl, s-triazole[1,5-a]pyridyl, imidazo[1,2-c]pyrimidinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,5-a]pyrazinyl, imidazo[1,5-a]pyrimidinyl, imidazo[1,2-b]-pyridazinyl, s-triazolo[4,3-a]pyrimidinyl, imidazo[5,1-b]oxazolyl and imidazo[2,1-b]oxazolyl. Other specific examples of such ring systems include, for example, [1H]-pyrrolo[2,1-c]oxazinyl, [3H]-oxazolo[3,4-a]pyridyl, [6H]-pyrrolo[2,1-c]oxazinyl and pyrido[2,1-c][1,4]oxazinyl. Other specific examples of 5/5- bicyclic ring systems are imidazooxazolyl or imidazothiazolyl, in particular imidazo[5,1-b]thiazolyl, imidazo[2,1-b]thiazolyl, imidazo[5,1-b]oxazolyl or imidazo[2,1-b]oxazolyl.

Examples of **–(1-6C)alkylHET2** include any one of the above particular values for HET2 attached to any value of (1-6C)alkyl, and thus includes for example (optionally substituted) indolylmethyl, indolylethyl, indolylpropyl, indolylbutyl and indoylhexyl.

The nomenclature used is that found in, for example, "Heterocyclic Compounds (Systems with bridgehead nitrogen)", W.L.Mosby (Interscience Publishers Inc., New York), 1961, Parts 1 and 2.

Particular values for optional substituents on AR1, AR2, HET1 and HET2 are 1, 2, 3, 4 or 5 substituents independently selected from cyano, halo, (1-6C)alkyl, halo(1-6C)alkyl, dihalo(1-6C)alkyl, trifluoromethyl, (1-6C)alkoxy, carboxy(1-6C)alkyl, carboxy(1-6C)alkoxy, hydroxy, amino, (1-6C)alkylamino, di(1-6C)alkylamino, $-CONH_2$, –CONH(1-6C)alkyl, -CONdi(1-6C)alkyl, –NHCO(1-6C)alkyl, $-S(O)_2NH_2$, $–SO_2NH$(1-6C)alkyl, $-SO_2N$di(1-6C)alkyl, $–NHSO_2$(1-6C)alkyl, -CO(1-6C)alkyl, $-CO_2$(1-6C)alkyl and –OCO(1-6C)alkyl.

Further particular values for optional substituents on AR1, AR2, HET1 and HET2 are 1, 2 or 3, substituents independently selected from cyano, halo, (1-6C)alkyl, halo(1-6C)alkyl, dihalo(1-6C)alkyl, trifluoromethyl, (1-6C)alkoxy, carboxy(1-4C)alkyl, carboxy(1-6C)alkoxy, hydroxy, amino, (1-6C)alkylamino, $-CONH_2$, –CONH(1-6C)alkyl, -CONdi(1-6C)alkyl, –

NHCO(1-6C)alkyl, $-S(O)_2NH_2$, $-SO_2NH$(1-6C)alkyl, $-NHSO_2$(1-6C)alkyl.

Further particular values for optional substituents on AR1, AR2, HET1 and HET2 are 1 or 2 substituents independently selected from cyano, halo, methyl, ethyl, fluoromethyl, difluoromethyl, chloromethyl, trifluoromethyl, methoxy, carboxymethyl, carboxymethoxy, hydroxy, amino, methylamino, ethylamino, $-CONH_2$, –CONHMe, –NHCOMe, $-S(O)_2NH_2$, $-SO_2NHMe$ and $-NHSO_2Me$.

Further particular values for optional substituents on AR1, AR2, HET1 and HET2 are 1 or 2 substituents independently selected from cyano, fluoro, chloro, methyl, ethyl, fluoromethyl, difluoromethyl, chloromethyl, trifluoromethyl, methoxy, carboxymethyl, carboxymethoxy, hydroxy, $-CONH_2$ and $-S(O)_2NH_2$.

If not stated elsewhere, suitable optional substituents for a particular group are those as stated for similar groups herein.

A compound of formula (I) may form stable acid or basic salts, and in such cases administration of a compound as a salt may be appropriate, and pharmaceutically acceptable salts may be made by conventional methods such as those described following.

Suitable pharmaceutically-acceptable salts include acid addition salts such as methanesulfonate, tosylate, α-glycerophosphate, fumarate, hydrochloride, citrate, maleate, tartrate and (less preferably) hydrobromide. Also suitable are salts formed with phosphoric and sulfuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, N-methylpiperidine, N-ethylpiperidine, procaine, dibenzylamine, N,N-dibenzylethylamine, tris-(2-hydroxyethyl)amine, N-methyl d-glucamine and amino acids such as lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically-acceptable salt is the sodium salt.

However, to facilitate isolation of the salt during preparation, salts which are less soluble in the chosen solvent may be preferred whether pharmaceutically-acceptable or not.

Within the present invention it is to be understood that a compound of the formula (I) or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which inhibits DPP-IV activity and is not to be limited merely to any one tautomeric form utilised within the

formulae drawings.

It will be appreciated by those skilled in the art that certain compounds of formula (I) contain asymmetrically substituted carbon and/or sulphur atoms, and accordingly may exist in, and be isolated in, optically-active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic or stereoisomeric form, or mixtures thereof, which form possesses properties useful in the inhibition of DPP-IV activity, it being well known in the art how to prepare optically-active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, by enzymatic resolution, by biotransformation, or by chromatographic separation using a chiral stationary phase) and how to determine efficacy for the inhibition of DPP-IV activity by the standard tests described hereinafter.

It is also to be understood that certain compounds of the formula (I) and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which inhibit DPP-IV activity.

As stated before, we have discovered a range of compounds that have good DPP-IV inhibitory activity. They have good physical and/or pharmacokinetic properties in general. The following compounds possess preferred pharmaceutical and/or physical and/or pharmacokinetic properties.

Particular aspects of the invention comprise a compound of formula (I), or a pharmaceutically-acceptable salt thereof, wherein the substituents Ar, R^1 to R^9 and other substituents mentioned above have values defined hereinbefore, or any of the following values (which may be used where appropriate with any of the definitions and embodiments disclosed hereinbefore or hereinafter):

In one embodiment of the invention are provided compounds of formula (I), in an alternative embodiment are provided pharmaceutically-acceptable salts of compounds of formula (I).

Particular values of variable groups are as follows. Such values may be used where appropriate with any of the other values, definitions, claims or embodiments defined hereinbefore or hereinafter.

1) Ar is unsubstituted phenyl

2) Ar is phenyl substituted with 1 group R^9

3) Ar is phenyl substituted with 2 groups independently selected from R^9

4) Ar is phenyl substituted with 4 groups independently selected from R^9

5) R^9 is halo, preferably fluoro

6) R^9 is (1-6C)alkyl (optionally substituted with 1-5 halo), for example (1-4C)alkyl (optionally substituted with 1-5 halo), such as methyl, fluoromethyl, difluoromethyl or trifluoromethyl

7) R^9 is (1-6C)alkoxy (optionally substituted with 1-5 halo), for example (1-4C)alkoxy (optionally substituted with 1-5 halo), such as methoxy, fluoromethoxy, difluoromethxoy or trifluoromethoxy

8) R^9 is cyano

9) R^1 is hydrogen

10) R^1 is (1-6C)alkyl, for example (1-4C)alkyl, such as methyl

11) R^5 is hydrogen or methyl

12) R^5 is hydrogen

13) R^6 is hydrogen or methyl

14) R^6 is hydrogen

15) R^7 is hydrogen or methyl

16) R^7 is hydrogen

17) R^8 is hydrogen or methyl

18) R^8 is hydrogen

19) R^3 and R^4 together form a ring as defined by AR2, HET1 or HET2

20) R^3 and R^4 together form a ring as defined by AR2

21) R^3 and R^4 together form a ring as defined by HET1

22) R^3 and R^4 together form a ring as defined by HET2

23) R^3 and R^4 are independently selected from hydrogen, (1-6C)alkyl, -(1-6C)alkyl(3-8C)cycloalkyl, -(1-6C)alkyl(3-8C)cycloalkenyl, -(1-6C)alkylAR1, -(1-6C)alkylAR2, -(1-6C)alkylHET1 and -(1-6C)alkylHET2

24) R^3 is hydrogen and R^4 is -(1-6C)alkylAR1 such as benzyl

25) R^3 is hydrogen and R^4 is -(1-6C)alkylAR2

26) R^3 is hydrogen and R^4 is -(1-6C)alkylHET1

27) R^3 is hydrogen and R^4 is -(1-6C)alkylHET2

28) R^3 is (1-6C)alkyl, such as (1-4C)alkyl, for example methyl and R^4 is selected from -(1-6C)alkyl(3-8C)cycloalkyl, -(1-6C)alkyl(3-8C)cycloalkenyl, -(1-6C)alkylAR1, -(1-6C)alkylAR2, -(1-6C)alkylHET1 and -(1-6C)alkylHET2

29) R^3 is hydrogen and R^4 is selected from -(1-6C)alkyl(3-8C)cycloalkyl, -(1-6C)alkyl(3-8C)cycloalkenyl, -(1-6C)alkylAR1, -(1-6C)alkylAR2, -(1-6C)alkylHET1 and -(1-6C)alkylHET2

30) R^1 and R^2 may together form a (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkylring or a ring defined by HET1; wherein a ring comprising R^1 and R^2 is optionally substituted by 1 or 2 substituents independently selected from halo, (1-6C)alkyl, halo(1-6C)alkyl, (1-6C)alkoxy, cyano, carboxy, carboxy(1-6C)alkyl, –CO(1-6C)alkyl, –CO_2(1-6C)alkyl, (1-6C)alkylamino, di-(1-6C)alkylamino, –NHCO(1-6C)alkyl, –CONH(1-6C)alkyl, -CONdi-(1-6C)alkyl and HET1

31) R^2 is selected from hydrogen, (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, and (6-12C)tricycloalkyl

32) R^2 is selected from AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylAR2, -(1-6C)alkyl(3-8C)cycloalkyl, -(1-6C)alkylHET1 and -(1-6C)alkylHET2

33) R^2 is selected from -(1-6C)alkylCO_2(1-6C)alkyl, -(1-6C)alkylCO_2(3-8C)cycloalkyl, -(1-6C)alkylCO_2AR1, -(1-6C)alkylCO_2HET1, -(1-6C)alkylOCO(1-6C)alkyl, -(1-6C)alkylOCO(3-8C)cycloalkyl, -(1-6C)alkylOCOAR1 and -(1-6C)alkylOCOHET1

34) R^2 is selected from -(1-6C)alkylCO(1-6C)alkyl, -(1-6C)alkylCO(3-8C)cycloalkyl, -(1-6C)alkylCOAR1 and -(1-6C)alkylCOHET1

35) R^2 is selected from -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCO(3-8C)cycloalkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONH(3-8C)cycloalkyl, -(1-6C)alkylCON-di(1-6C)alkyl and -(1-6C)alkylCONHAR1

36) R^2 is selected from -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylN-di(1-6C)alkyl, -(1-6C)alkylNHAR1 and -(1-6C)alkylNH(HET1)

37) R^2 is selected from -(1-6C)alkylNHSO_2(1-6C)alkyl, -(1-6C)alkylSO_2NH(1-6C)alkyl and -(1-6C)alkylSO_2N-di(1-6C)alkyl

38) R^2 is selected from hydrogen, (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCON-di(1-6C)alkyl, -(1-6C)alkylCONHAR1, -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylN-di(1-6C)alkyl ,

-(1-6C)alkylNHAR1, -(1-6C)alkylNH(HET1), -(1-6C)alkylNHSO$_2$(1-6C)alkyl, -(1-6C)alkylSO$_2$NH(1-6C)alkyl and -(1-6C)alkylSO$_2$N-di(1-6C)alkyl

39) R^2 is selected from (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONHAR1, -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylNHAR1, -(1-6C)alkylNH(HET1), -(1-6C)alkylNHSO$_2$(1-6C)alkyl and -(1-6C)alkylSO$_2$NH(1-6C)alkyl

40) R^2 is selected from (1-6C)alkyl, cyclohexyl, norbonyl, adamantyl, phenyl (optionally substituted by 1 or 2 substituents selected from fluoro, chloro, trifluoromethyl, methanesulfonamido, carboxymethyl, -SO$_2$NH$_2$ and -SO$_2$NHMe), benzyl (optionally substituted by 1 or 2 substituents selected from fluoro, chloro, trifluoromethyl, methanesulfonamido, carboxymethyl, -SO$_2$NH$_2$ and -SO$_2$NHMe), -(1-4C)alkylCONH(1-4C)alkyl, -(1-4C)alkylCONHPh (optionally substituted by 1 or 2 substituents selected from fluoro, chloro, trifluoromethyl, methanesulfonamido, carboxymethyl, -SO$_2$NH$_2$ and -SO$_2$NHMe), and -(1-4C)alkylNHSO$_2$(1-4C)alkyl

41) R^1 and R^2 together form a (3-8C)cycloalkyl , (5-12C)bicycloalkyl, or (6-12C)tricycloalkyl ring

42) R^1 and R^2 together form a ring defined by HET1, optionally substituted by 1 or 2 substituents independently selected from halo, (1-6C)alkyl, halo(1-6C)alkyl, (1-6C)alkoxy, cyano, carboxy, carboxy(1-6C)alkyl, –CO(1-6C)alkyl, –CO$_2$(1-6C)alkyl, (1-6C)alkylamino, di-(1-6C)alkylamino, –NHCO(1-6C)alkyl, –CONH(1-6C)alkyl, -CONdi-(1-6C)alkyl and HET1

43) R^1 and R^2 together form a furyl, pyrrolyl, thiophenyl, pyrazolyl, imidazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, 1,2,3- & 1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxazinyl, oxadiazolyl, thiazolyl, isothiazolyl, 1,2,4- and 1,3,4-thiadiazolyl, oxazoline, thiazoline, dihydropyrrolyl (especially 2,5-dihydropyrrol-4-yl), tetrahydropyridyl (especially 1,2,5,6-tetrahydropyrid-4-yl), tetrahydrofuranyl, , tetrahydrothienyl, 1-oxotetrahydrothienyl, 1,1-dioxotetrahydrothienyl, pyrrolidinyl, oxazolidine, thiazolidine, morpholinyl, thiomorpholinyl, piperazinyl, imidazolyl, piperidyl, 1,3-dioxolan-4-yl, 1,3-dioxan-4-yl, 1,3-dioxan-5-yl or 1,4-dioxan-2-yl ring, optionally substituted as hereinbefore described

44) R^1 and R^2 together form a furyl, pyrrolyl, thiophenyl, pyrazolyl, imidazolyl, pyridyl, pyrimidyl, oxazoline, thiazoline, dihydropyrrolyl (especially 2,5-dihydropyrrol-4-yl), tetrahydropyridyl (especially 1,2,5,6-tetrahydropyrid-4-yl), tetrahydrofuranyl, ,

tetrahydrothienyl, 1-oxotetrahydrothienyl, 1,1-dioxotetrahydrothienyl, pyrrolidinyl, oxazolidine, thiazolidine, morpholinyl, thiomorpholinyl, piperazinyl, imidazolyl or piperidyl ring optionally substituted as hereinbefore described

45) R^1 and R^2 together form a dihydropyrrolyl (especially 2,5-dihydropyrrol-4-yl), tetrahydropyridyl (especially 1,2,5,6-tetrahydropyrid-4-yl), tetrahydrofuranyl, , tetrahydrothienyl, 1-oxotetrahydrothienyl, 1,1-dioxotetrahydrothienyl, pyrrolidinyl, oxazolidine, thiazolidine, morpholinyl, thiomorpholinyl, piperazinyl or piperidyl ring optionally substituted by 1 or 2 substituents independently selected from cyano, halo, (1-6C)alkyl, halo(1-6C)alkyl, dihalo(1-6C)alkyl, trifluoromethyl, (1-6C)alkoxy, carboxy(1-4C)alkyl, carboxy(1-6C)alkoxy, hydroxy, amino, (1-6C)alkylamino, $-CONH_2$, –CONH(1-6C)alkyl, -CONdi(1-6C)alkyl, –NHCO(1-6C)alkyl, $-S(O)_2NH_2$, $–SO_2NH$(1-6C)alkyl and $–NHSO_2$(1-6C)alkyl

46) R^1 and R^2 together form a tetrahydropyridyl (especially 1,2,5,6-tetrahydropyrid-4-yl), tetrahydrofuranyl, pyrrolidinyl, oxazolidine, thiazolidine, morpholinyl, thiomorpholinyl, piperazinyl or piperidyl ring optionally substituted by 1 or 2 substituents independently selected from cyano, halo, (1-6C)alkyl, halo(1-6C)alkyl, dihalo(1-6C)alkyl, trifluoromethyl, (1-6C)alkoxy, carboxy(1-4C)alkyl, carboxy(1-6C)alkoxy, hydroxy, amino, (1-6C)alkylamino, $-CONH_2$, –CONH(1-6C)alkyl, -CONdi(1-6C)alkyl, –NHCO(1-6C)alkyl, $-S(O)_2NH_2$, $–SO_2NH$(1-6C)alkyl and $–NHSO_2$(1-6C)alkyl

47) R^1 and R^2 together form a pyrrolidinyl, or piperidyl ring optionally substituted by 1 or 2 substituents independently selected from cyano, halo, (1-6C)alkyl, halo(1-6C)alkyl, dihalo(1-6C)alkyl, trifluoromethyl, (1-6C)alkoxy, carboxy(1-4C)alkyl, carboxy(1-6C)alkoxy, hydroxy, amino, (1-6C)alkylamino, $-CONH_2$, –CONH(1-6C)alkyl, -CONdi(1-6C)alkyl, –NHCO(1-6C)alkyl, $-S(O)_2NH_2$, $–SO_2NH$(1-6C)alkyl and $–NHSO_2$(1-6C)alkyl

48) R^1 and R^2 together form a pyrrolidinyl, or piperidyl ring optionally substituted by 1 or 2 substituents independently selected from cyano, halo, methyl, ethyl, fluoromethyl, difluoromethyl, chloromethyl, trifluoromethyl, methoxy, carboxymethyl, carboxymethoxy, hydroxy, amino, methylamino, ethylamino, $-CONH_2$, –CONHMe, –NHCOMe, $-S(O)_2NH_2$, $–SO_2NHMe$ and $–NHSO_2Me$

49) R^1 is hydrogen

50) R^1 is methyl

In one aspect of the invention is provided a compound of the formula (I) or a pharmaceutically acceptable salt thereof wherein

Ar is phenyl optionally substituted with 1 or 2 groups independently selected from R^9;

R^9 is selected from halo, methyl, methoxy and trifluoromethyl;

R^1 is hydrogen or methyl;

R^5 is hydrogen;

R^6 is hydrogen;

R^7 is hydrogen;

R^8 is hydrogen;

R^3 and R^4 together form a ring as defined by AR2, HET1 or HET2;

R^2 is selected from (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONHAR1, -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylNHAR1, -(1-6C)alkylNH(HET1), -(1-6C)alkylNHSO$_2$(1-6C)alkyl and -(1-6C)alkylSO$_2$NH(1-6C)alkyl.

In another aspect of the invention is provided a compound of the formula (I) or a pharmaceutically acceptable salt thereof wherein

Ar is phenyl optionally substituted with 1 or 2 groups independently selected from R^9;

R^9 is selected from halo, methyl, methoxy and trifluoromethyl;

R^1 is hydrogen or methyl;

R^5 is hydrogen;

R^6 is hydrogen;

R^7 is hydrogen;

R^8 is hydrogen;

R^3 and R^4 together form a ring as defined by AR2;

R^2 is selected from (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONHAR1, -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylNHAR1, -(1-6C)alkylNH(HET1), -(1-6C)alkylNHSO$_2$(1-6C)alkyl and -(1-6C)alkylSO$_2$NH(1-6C)alkyl.

In another aspect of the invention is provided a compound of the formula (I) or a pharmaceutically acceptable salt thereof wherein

Ar is phenyl optionally substituted with 1 or 2 groups independently selected from R^9;

R^9 is selected from halo, methyl, methoxy and trifluoromethyl;

R^1 is hydrogen or methyl;

R^5 is hydrogen;

R^6 is hydrogen;

R^7 is hydrogen;

R^8 is hydrogen;

R^3 and R^4 together form an indanyl ring;

R^2 is selected from (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONHAR1, -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylNHAR1, -(1-6C)alkylNH(HET1), -(1-6C)alkylNHSO$_2$(1-6C)alkyl and -(1-6C)alkylSO$_2$NH(1-6C)alkyl

In another aspect of the invention is provided a compound of the formula (I) or a pharmaceutically acceptable salt thereof wherein

Ar is phenyl, fluorophenyl or difluorophenyl;

R^1 is hydrogen;

R^5 is hydrogen;

R^6 is hydrogen;

R^7 is hydrogen;

R^8 is hydrogen;

R^3 and R^4 together form an indanyl ring;

R^2 is selected from (1-6C)alkyl, cyclohexyl, norbonyl, adamantyl, phenyl (optionally substituted by 1 or 2 substituents selected from fluoro, chloro, trifluoromethyl, methanesulfonamido, carboxymethyl, -SO$_2$NH$_2$ and -SO$_2$NHMe), benzyl (optionally substituted by 1 or 2 substituents selected from fluoro, chloro, trifluoromethyl, methanesulfonamido, carboxymethyl, -SO$_2$NH$_2$ and -SO$_2$NHMe), -(1-4C)alkylCONH(1-4C)alkyl, -(1-4C)alkylCONHPh (optionally substituted by 1 or 2 substituents selected from fluoro, chloro, trifluoromethyl, methanesulfonamido, carboxymethyl, -SO$_2$NH$_2$ and -SO$_2$NHMe), and -(1-4C)alkylNHSO$_2$(1-4C)alkyl.

In another aspect of the invention is provided a compound of the formula (I) or a pharmaceutically acceptable salt thereof wherein

Ar is phenyl optionally substituted with 1 or 2 groups independently selected from R^9;

R^9 is selected from halo, methyl, methoxy and trifluoromethyl;

R^1 is hydrogen or methyl;

R^5 is hydrogen;

R^6 is hydrogen;

R^7 is hydrogen;

R^8 is hydrogen;

R^3 is hydrogen and R^4 is selected from -(1-4C)alkyl(3-8C)cycloalkyl, -(1-4C)alkyl(3-8C)cycloalkenyl, -(1-4C)alkylAR1, -(1-4C)alkylAR2, -(1-4C)alkylHET1 and -(1-4C)alkylHET2;

R^2 is selected from (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONHAR1, -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylNHAR1, -(1-6C)alkylNH(HET1), -(1-6C)alkylNHSO$_2$(1-6C)alkyl and -(1-6C)alkylSO$_2$NH(1-6C)alkyl.

In another aspect of the invention is provided a compound of the formula (I) or a pharmaceutically acceptable salt thereof wherein

Ar is phenyl optionally substituted with 1 or 2 groups independently selected from R^9;

R^9 is selected from halo, methyl, methoxy and trifluoromethyl;

R^1 is hydrogen or methyl;

R^5 is hydrogen;

R^6 is hydrogen;

R^7 is hydrogen;

R^8 is hydrogen;

R^3 is hydrogen and R^4 is selected from -(1-4C)alkylAR1, -(1-4C)alkylAR2, -(1-4C)alkylHET1 and -(1-4C)alkylHET2;

R^2 is selected from (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONHAR1, -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylNHAR1, -(1-6C)alkylNH(HET1),

-(1-6C)alkylNHSO$_2$(1-6C)alkyl and -(1-6C)alkylSO$_2$NH(1-6C)alkyl.

In another aspect of the invention is provided a compound of the formula (I) or a pharmaceutically acceptable salt thereof wherein

Ar is phenyl optionally substituted with 1 or 2 groups independently selected from R^9;

R^9 is selected from halo, methyl, methoxy and trifluoromethyl;

R^1 is hydrogen or methyl;

R^5 is hydrogen;

R^6 is hydrogen;

R^7 is hydrogen;

R^8 is hydrogen;

R^3 is hydrogen and R^4 is selected from benzyl, (optionally substituted with 1 or 2 substituents selected from cyano, fluoro, chloro, methyl, ethyl, fluoromethyl, difluoromethyl, chloromethyl, trifluoromethyl, methoxy, carboxymethyl, carboxymethoxy, hydroxy, -CONH$_2$ and -S(O)$_2$NH$_2$;

R^2 is selected from (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONHAR1, -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylNHAR1, -(1-6C)alkylNH(HET1), -(1-6C)alkylNHSO$_2$(1-6C)alkyl and -(1-6C)alkylSO$_2$NH(1-6C)alkyl.

In another aspect of the invention is provided a compound of the formula (I) or a pharmaceutically acceptable salt thereof wherein

Ar is phenyl, fluorophenyl or difluorophenyl;

R^1 is hydrogen;

R^5 is hydrogen;

R^6 is hydrogen;

R^7 is hydrogen;

R^8 is hydrogen;

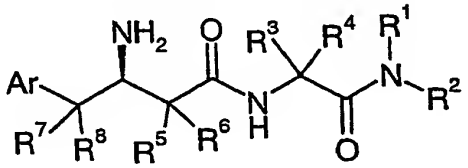
R^3 is hydrogen;

R^4 is benzyl;

R^2 is selected from (1-6C)alkyl, cyclohexyl, norbonyl, adamantyl, phenyl (optionally substituted by 1 or 2 substituents selected from fluoro, chloro, trifluoromethyl,

methanesulfonamido, carboxymethyl, -SO_2NH_2 and -SO_2NHMe), benzyl (optionally substituted by 1 or 2 substituents selected from fluoro, chloro, trifluoromethyl, methanesulfonamido, carboxymethyl, -SO_2NH_2 and -SO_2NHMe), -(1-4C)alkylCONH(1-4C)alkyl, -(1-4C)alkylCONHPh (optionally substituted by 1 or 2 substituents selected from fluoro, chloro, trifluoromethyl, methanesulfonamido, carboxymethyl, -SO_2NH_2 and -SO_2NHMe), and -(1-4C)alkylNHSO$_2$(1-4C)alkyl.

Particular compounds of the invention are of the formula (Ia):



(IA)

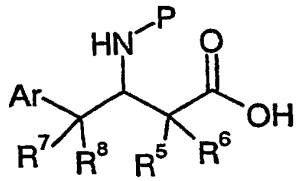
wherein Ar, R^1 to R^8 are as defined in any one of the definitions, embodiments or aspects contained herein before or hereinafter.

Process

A compound of formula (I) and its pharmaceutically-acceptable salts may be prepared by any process known to be applicable to the preparation of chemically related compounds. Such processes, when used to prepare a compound of the formula (I), or a pharmaceutically-acceptable salt thereof, are provided as a further feature of the invention.

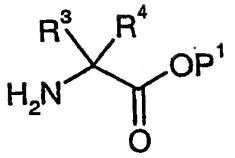
In a further aspect the present invention also provides that the compounds of the formulae (I) and pharmaceutically-acceptable salts thereof, can be prepared by a process **(a)** to **(d)** as follows (wherein the variables are as defined hereinbefore or after unless otherwise stated) :

a) Coupling a compound of the formula (II) wherein P is a protecting group



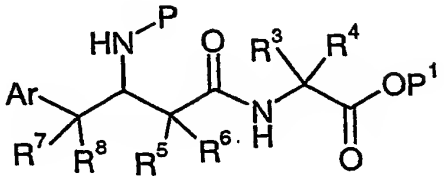
(II)

with a compound of the formula (III), wherein P^1 is a protecting group;



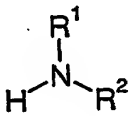
(III)

to give a compound of the formula (IV);



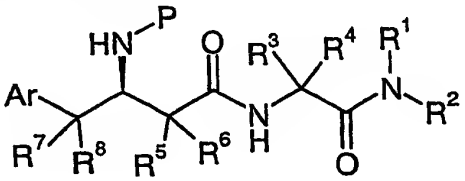
(IV)

b) removing the protecting group P^1 and coupling the resultant acid with a compound of the formula (V)



(V)

to give a compound of the formula (VI); and



(VI)

c) removing the protecting group P to give a compound of the formula (I);

d) optionally forming a pharmaceutically acceptable salt.

Compounds of the formula (II) are generally commercially available or may be made by processes known in the art for making β-amino acids. Suitably the protecting group P is a carbamate protecting group such as a BOC group.

Compounds of the formula (III) are generally commercially available or may be made by processes known in the art for making protected forms of amino acids. Suitably the protecting group P^1 is an alkyl group, such as methyl.

Suitable coupling conditions for step a) are any of those known in the art for coupling together acids and bases for example standard peptide coupling reagents known in the art, or for example carbonyldiimidazole, 1-ethyl-3-(3-dimethylaminopropyl)carbodi-imide

hydrochloride (EDCI) and dicyclohexyl-carbodiimide (DCCI), optionally in the presence of a catalyst such as 1-hydroxybenzotriazole, dimethylaminopyridine or 4-pyrrolidinopyridine, optionally in the presence of a base for example triethylamine, di-isopropylethylamine, pyridine, or 2,6-di-*alkyl*-pyridines such as 2,6-lutidine or 2,6-di-*tert*-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

Removal of the proptecting group P^1 may be achieved by any suitable method known in the art. Where P^1 is an alkyl group, the ester may be hydrolysed under acid or basic conditions, for example using alkali bases such as sodium hydroxide or lithium hydroxide.

Coupling the resulting carboxylic acid with the compound of the formula (IV) may be carried out using similar conditions to those used in step a).

Compounds of the formula (IV) are generally commercially available or may be made by processes known in the art.

Removal of the proptecting group P may be achieved by any suitable method known in the art. Where P is a carbamate group such as a BOC group, hydrolysis of the BOC group may be achieved using aqueous acid, for example a solution of aqueous HCl in dioxan. Conditions suitable for removing the protecting group P, such as treatment with an acid such as HCl, may result information of a salt of a compound of the formula (I), which may optionally be treated to give the free base form or to give an alternative (pharmaceutically acceptable) salt form.

If not commercially available, the necessary starting materials for the procedures such as those described above may be made by procedures which are selected from standard organic chemical techniques, techniques which are analogous to the synthesis of known, structurally similar compounds, techniques which are described or illustrated in the references given above, or techniques which are analogous to the above described procedure or the procedures described in the examples.

It is noted that many of the starting materials for synthetic methods as described above are commercially available and/or widely reported in the scientific literature, or could be made from commercially available compounds using adaptations of processes reported in the scientific literature. The reader is further referred to Advanced Organic Chemistry, 4th Edition, by Jerry March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents.

It will be appreciated that some intermediates to compounds of the formula (I) are also novel and these are provided as separate independent aspects of the invention.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in compounds. The instances where protection is necessary or desirable are known to those skilled in the art, as are suitable methods for such protection. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Greene, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991).

Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Thus, if reactants include, for example, groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

Examples of a suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, a silyl group such as trimethylsilyl or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively a silyl group such as trimethylsilyl may be removed, for example, by fluoride or by aqueous acid; or an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation in the presence of a catalyst such as palladium-on-carbon.

A suitable protecting group for an amino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or tert-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a

suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine or 2-hydroxyethylamine, or with hydrazine.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

Resins may also be used as a protecting group.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art, or they may be removed during a later reaction step or work-up.

The skilled organic chemist will be able to use and adapt the information contained and referenced within the above references, and accompanying Examples therein and also the Examples herein, to obtain necessary starting materials, and products.

The removal of any protecting groups and the formation of a pharmaceutically-acceptable salt are within the skill of an ordinary organic chemist using standard techniques. Furthermore, details on the these steps has been provided hereinbefore.

When an optically active form of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using an optically active starting material (formed, for example, by asymmetric induction of a suitable reaction step), or by resolution of a racemic form of the compound or intermediate using a standard procedure, or by chromatographic separation of diastereoisomers (when produced). Enzymatic techniques may also be useful for the preparation of optically active compounds and/or intermediates.

Similarly, when a pure regioisomer of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using a pure regioisomer as a starting material, or by resolution of a mixture of the regioisomers or intermediates using a standard procedure.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I) as defined hereinbefore or a pharmaceutically-acceptable salt thereof, in association with a pharmaceutically-acceptable excipient or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation

products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

According to a further aspect of the present invention there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

We have found that compounds of the present invention inhibit DPP-IV activity and are therefore of interest for their blood glucose-lowering effects.

A further feature of the present invention is a compound of formula (I) and

pharmaceutically-acceptable salts thereof for use as a medicament.

Conveniently this is a compound of formula (I), or a pharmaceutically-acceptable salt thereof, for use as a medicament for producing an inhibition of DPP-IV activity in a warm-blooded animal such as a human being.

Particularly this is a compound of formula (I), or a pharmaceutically-acceptable salt thereof, for use as a medicament for treating diabetes mellitus in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically-acceptable salt thereof in the manufacture of a medicament for use in the production of an inhibition of DPP-IV activity in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically-acceptable salt thereof in the manufacture of a medicament for use in the treatment of diabetes mellitus in a warm-blooded animal such as a human being.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I) as defined hereinbefore or a pharmaceutically-acceptable salt thereof, in association with a pharmaceutically-acceptable excipient or carrier for use in producing an inhibition of DPP-IV activity in an warm-blooded animal, such as a human being.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I) as defined hereinbefore or a pharmaceutically-acceptable salt thereof, in association with a pharmaceutically-acceptable excipient or carrier for use in the treatment of diabetes mellitus in an warm-blooded animal, such as a human being.

According to a further feature of the invention there is provided a method for producing an inhibition of DPP-IV activity in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically-acceptable salt thereof as defined hereinbefore.

According to a further feature of the invention there is provided a method of treating diabetes mellitus in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula

(I) or a pharmaceutically-acceptable salt thereof as defined hereinbefore.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

As stated above compounds defined in the present invention are of interest for their ability to inhibit the activity of DPP-IV. A compound of the invention may therefore be useful for the prevention, delay or treatment of a range of disease states including diabetes mellitus, more specifically type 2 diabetes mellitus (T2DM) and complications arising there from (for example retinopathy, neuropathy and nephropathy), impaired glucose tolerance (IGT), conditions of impaired fasting glucose, metabolic acidosis, ketosis, dysmetabolic syndrome, arthritis, osteoporosis, obesity and obesity related disorders, peripheral vascular disease, (including intermittent claudication), cardiac failure and certain cardiac myopathies, myocardial ischaemia, cerebral ischaemia and reperfusion, muscle weakness, hyperlipidaemias, Alzheimer's disease , atherosclerosis, infertility, polycystic ovary syndrome, various immunomodulatory diseases (such as psoriasis), HIV infection, inflammatory bowel syndrome, inflammatory bowel disease (such as Crohn's disease and ulcerative colitis.

In a further aspect, compounds of the formula (I) or their pharmaceutically acceptable salts may be administered in combination with other therapeutic agents in order to prevent, delay or treat the various disease states in which DPP-IV activity is implicated, including but not limited to those disease states listed above. For example, in order to prevent, delay or treat type 2 diabetes mellitus, the compounds of the present invention or their pharmaceutically-acceptable salts may be administered in combination with a therapeutically effective amount of one or more other compounds of the formula (I) and/or one or more types of antidiabetic agent. Suitable types of antidiabetic agents (or antihyperglycemic agents) include sulfonylureas and other insulin secretagogues, PPAR γ agonists (thiazolidine dione (TZD) and non-TZD), GSK3 inhibitors and other insulin sensitisers, biguanides, glucosidase inhibitors, SGLT2 inhibitors, PPAR α/γ dual agonists, aP2 inhibitors, glycogen phosphorylase inhibitors, glucokinase activators, PDH activators, advanced glycosylation end

product inhibitors, meglitinides and insulin.

In addition to its use in therapeutic medicine, compounds of formula (I) and their pharmaceutically-acceptable salts are also useful as pharmacological tools in the development and standardisation of in-vitro and in-vivo test systems for the evaluation of the effects of inhibitors of DPP-IV activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

As indicated above, all of the compounds, and their corresponding pharmaceutically-acceptable salts, are useful in inhibiting DPP-IV. The ability of the compounds of formula (I), and their corresponding pharmaceutically-acceptable acid addition salts, to inhibit DPP-IV may be demonstrated employing the caco-2 DPP-IV Assay which measures the ability of test compounds to inhibit DPP-IV activity from human colonic carcinoma cell extracts. The human colonic carcinoma cell line Caco-2 was obtained from the American Type Culture Collection (ATCC HTB 37). Differentiation of the cells to induce DPP-IV expression was accomplished as described by Reisher, et al. (Proc. Natl. Acad. Sci., Vol. 90, pgs. 5757-5761 (1993)). Cell extract is prepared from cells solubilized in 10mM Tris HCl, 0.15 M NaCl, 0.04 t.i.u.aprotinin, 0.5% nonidet-P40, pH 8.0, which is centrifuged at 35,000 g for 30 min at 4°C to remove cell debris.

The colorimetric assay is conducted by adding 20 µg solubilized Caco-2 protein or purified porcine kidney DPP-IV, in a final volume of 10ul in assay buffer (25 mM Tris HCl pH 7.4, 140mM NaCl, 10 mM KCl,0.1% Triton-x-100) to microtiter plate wells. After a 10 min. incubation at room temperature, the reaction is initiated by adding 10 µl of 0.5 mM substrate (H-Glycine -Proline-pNA; pNA is p-nitroaniline). The final assay volume is 100µl. The reaction is carried out at room temperature for 10 minutes after which time a 20 µl volume of sodium acetate buffer pH 4.5 is added to stop the reaction. Test compounds are typically added as 10 µl additions A standard curve of free p-nitroaniline is generated using 0-500 µM solutions of free pNA in assay buffer. The curve generated is linear and is used for interpolation of substrate consumption (catalytic activity in nmoles substrate cleaved/min). The endpoint is determined by measuring absorbance at 405 nm in a Labsystems microtiter plate reader.

Activity of CaCo2 extract is also measured employing a modified version of the assay described in Kubota, et al. (Clin. Exp.Immunol., Vol.89, pgs. 192-197 (1992)). The assay is conducted by adding 10 µg solubilized Caco-2 protein, in a final volume of 10 ul assay buffer (25 mMHEPES, 140 mM NaCl, 80 mM MgCl2, 0.1% Triton X-100, pH 7.4) to micro titer

plate wells. After 10 min incubation at room temperature, the reaction is initiated by the addition of 10 µl of incubation buffer containing 0.5 mM substrate (H-Glycine-Proline-AMC; AMC is 7-amino-40-methylcoumarin). The plates are at room temperature (in the dark) for 10 min. Test compounds are typically added as 10 µl additions and the final assay buffer volume is 100µl. The reaction is initiated by adding 10 µl of 0.5 mM substrate Gly-Pro-7-amino-4-trifluoromethylcoumarin for 10 minutes after which time a 20 µl volume of sodium acetate buffer pH4.5 is added to stop the reaction. After the 10 min. reaction, florescence is measured using a Tecan Ultra fluorimeter (Excitation 360 nm Emission 465 nm). .A standard curve of free AMC is generated using 0-50 µM solutions of free AMC in assay buffer. The curve generated is linear and is used for interpolation of substrate consumption (catalytic activity in nmoles substrate cleaved/min). The potency of the test compounds as DPP-IV inhibitors, expressed as IC_{50}, is calculated from 11-point, dose-response curves using a 4 parameter logistic function.

Using this assay the compounds generally show activity with $IC_{50} < 100$ µM. Example 1 showed an $IC_{50} = 0.46$ µM.

The ability of the compounds of formula I, and their corresponding pharmaceutically acceptable acid addition salts, to inhibit DPP-IV may also be demonstrated by measuring the effects of test compounds on DPP-IV activity in human and rat plasma employing a modified version of the assay described above. Briefly, 5-10 µl of plasma are added to 96-well flat-bottom microtiter plates instead of CaCo2 extract, final assay volume is 100µl . As with the previous assay, the potency of the test compounds as DPP-IV inhibitors, expressed as IC_{50}, is calculated from 11-point, dose-response curves using a 4 parameter logistic function.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Examples

The invention will now be illustrated by the following Examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C and under an atmosphere of an inert gas such as argon;

(ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mmHg) with a bath temperature of up to 60°C;

(iii) chromatography means flash chromatography on silica gel; where a Biotage cartridge is referred to this means a cartridge containing KP-SIL™ silica, 60Å, particle size 32-63mM, supplied by Biotage, a division of Dyax Corp., 1500 Avon Street Extended, Charlottesville, VA 22902, USA;

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vi) where given, NMR data (^1H) is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz (unless otherwise stated) using perdeuterio dimethyl sulphoxide (DMSO-δ_6) as solvent;

(vii) chemical symbols have their usual meanings; SI units and symbols are used;

(viii) solvent ratios are given in volume : volume (v/v) terms;

(ix) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (CI) mode using a direct exposure probe; where indicated ionisation was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for m/z are given; generally, only ions which indicate the parent mass are reported;

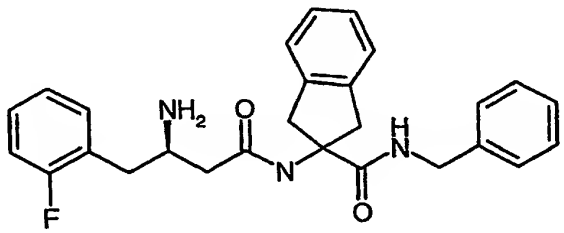
(x) The following abbreviations are used:

Et_2O	diethyl ether
DMF	dimethylformamide;
DCM	dichloromethane
DME	dimethoxyethane;
MeOH	methanol
EtOH	ethanol;
H_2O	water;
TFA	trifluoroacetic acid
THF	tetrahydrofuran
DMSO	dimethylsulfoxide
HOBt	1-hydroxybenzotriazole

EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodi-imide hydrochloride
DIPEA	diisopropylethylamine
DEAD	diethylazodicarboxylate

Each of the following Examples is provided as a separate and independent aspect of the invention.

Example 1: 2-{[(3*R*)-3-Amino-4-(2-fluorophenyl)butanoyl]amino}-*N*-benzylindane-2-carboxamide hydrogen chloride salt



To a stirred solution of (*R*)-3-*tert*-butoxycarbonylamino-4-(2-fluoro-phenyl)-butyric acid (0.296 g, 1.0 mmol) in DCM (20 mL) was added sequentially HOBt (0.16 g, 1.2 mmol), EDCI (0.23 g, 1.2 mmol), 2-amino-indan-2-carboxylic acid methyl ester (Kotha, S and Kuki, A *Tetrahedron Lett.*, 1992, 33, (12) 1565) (0.277 g, 1.0 mmol) and triethylamine (0.28 ml, 2.0 mmol). The mixture was stirred at ambient temperature for 16 h. The reaction mixture was then washed sequentially with 2M HCl (50 ml), aqueous sodium bicarbonate (50 ml) and brine (100 ml). The organic phase was separated, dried with magnesium sulphate and concentrated under reduced pressure to leave a pale yellow gum. The residue was purified by flash silica gel chromatography (ethyl acetate) to give methyl 2-{[3*R*)-3-[*tert*-butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoyl}-indane-2-carboxylate methyl ester (325 mg, 69%) as a colourless solid. ^{1}H NMR ($CDCl_3$): 1.35 (s, 9H), 2.26-2.45 (m, 2H), 2.88-2.92 (m, 2H), 3.20-3.29 (m, 2H), 3.62-3.71 (m, 2H), 3.76 (s, 3H), 6.32 (brs, 1H), 6.95-7.02 (m, 2H), 7.14 –7.20 (m, 6H); MS m/z 493 (M+Na).

A solution of this material (0.292 g, 0.598 mmol) in THF (10 ml) and water (3 ml) was treated with a solution of lithium hydroxide hydrate (50mg 1.19 mmol) in water (1 ml). The reaction mixture was allowed to stir at ambient temperature for 16 hours. The mixture was concentrated under reduced pressure and the aqueous residue was acidified to pH 2 with potassium hydrogen sulfate. The aqueous layer was extracted with ethyl acetate (2 x 100 ml)

and the organic phase separated. The combined organics was dried with magnesium sulfate and concentrated under reduced pressure to leave 2-{[*3R*)-3-[*tert*-butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoyl}-indane-2-carboxylic acid as a colourless solid (0.241 g, 94%). ^{1}H NMR (DMSO): 1.23 (s, 9H), 2.22 (d, 2H), 2.55-2.62 (m, 1H), 2.70-2.82 (m, 2H), 3.11-3.25 (m, 2H), 3.39-3.53 (m, 2H), 3.91-4.01 (brm, 1H), 6.60 (d, 1H), 7.03-7.20 (m, 8H), 8.44 (s, 1H), 12.29 (brs, 1H); MS m/z 455 $(MH)^-$.

EDCI (51 mg, 0.27 mmol) followed by HOBt (36 mg, 0.27 mmol) were added to a solution of this acid (0.101 g, 0.22 mmol) in DCM. The mixture was stirred for 2-3 minutes before the addition of triethylamine (30 µl, 0.22 mmol) and benzylamine (20 µl, 0.22 mmol). The reaction mixture was stirred at ambient temperature for 16 h. The reaction mixture was then washed sequentially with 2M HCl (50 ml) and brine (50 ml). The organic phase was separated, dried with magnesium sulphate and concentrated under reduced pressure to leave a colourless solid. The residue was purified by flash silica gel chromatography (ethyl acetate:isohexane 2:3) to give *Tert*-butyl[(1*R*)-3-(2-[(benzylamino)carbonyl]-2,3-dihydro-1*H*-inden-2-yl}amino)-1-(2-fluorobenzyl)-3-oxopropyl]carbamate (104 mg, 86%) as a colourless solid. ^{1}H NMR (DMSO): 1.23 (s, 9H), 2.25 (d, 2H), 2.55-2.62 (m, 1H), 2.70-2.77 (m,1H), 3.13-3.25 (m, 2H), 3.44-3.53 (m, 2H), 3.94-4.04 (m, 1H), 4.16-4.35 (m, 1H), 6.61 (d, 1H), 7.01-7.18 (m, 13H), 8.17 (t, 1H), 8.25 (s, 1H); MS m/z 568 (M+Na).

4M HCl in dioxan was added to this solid (104 mg, 0.191 mmol) and the mixture was stirred for 2 hours. The solvent was evaporated under reduced pressure and the residue triturated with ether. The ether was evaporated to afford the title compound as a colourless solid (88 mg, 96%). MS ESP+ m/z 360, 362; ESP- m/z 336, 338. ^{1}H NMR (DMSO): 2.78-2.85 (m, 2H), 2.95-3.02 (m, 2H), 3.10.3.25 (m, 3H), 3.51-3.57 (m, 5H), 4.23-4.27 (m, 2H), 7.05-7.27 (m, 13H), 8.16 (brs 2H), 8.37 (t, 1H), 8.63 (s, 1H); MS m/z 445 $(MH)^+$.

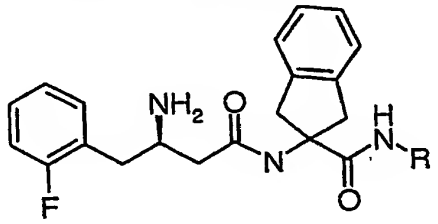
Examples 2-4

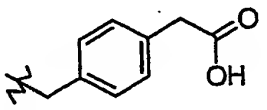
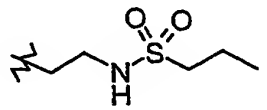
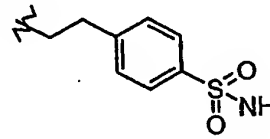
The following examples were made by an analogous method to Example 1 using the appropriate amine starting materials (commercially available for Examples 3 and 4; for Example 2 see CAS no. [479586-24-8] - reactant in Patent Application WO 2003045382) in place of benzylamine.

Example 2: [4-({[(2-{[(3*R*)-3-Amino-4-(2-fluorophenyl)butanoyl]amino}-2,3-dihydro-1*H*-inden-2-yl)carbonyl]amino}methyl)phenyl]acetic acid

Example 3: 2-{[(3*R*)-3-Amino-4-(2-fluorophenyl)butanoyl]amino}-*N*-{2-[(propylsulfonyl)amino]ethyl}indane-2-carboxamide

Example 4: 2-{[(3*R*)-3-Amino-4-(2-fluorophenyl)butanoyl]amino}-*N*-{2-[4-(aminosulfonyl)phenyl]ethyl}indane-2-carboxamide



Example	R	^{1}H NMR (DMSO)	MS m/z
2		2.35-2.41 (m, 2H), 2.70-2.80 (m, 1H), 2.90-2.97 (m, 1H), 3.08-3.23 (m, 2H), 3.35-3.60 (m, 5H), 4.20-4.24 (m,1H), 7.05-7.32 (m, 12H), 7.95 (brs, 2H), 8.30 (t, 1H), 8.57 (s, 1H)	504 $(MH)^+$
3		0.95 (t, 3H), 1.60-1.70 (m, 2H), 2.41-2.43 (m, 2H), 2.77-2.84 (m, 1H), 2.90-2.95 (m, 5H), 3.07-3.17 (m, 4H), 3.38-3.48 (m, 2H), 3.60-3.66 (m, 1H), 6.95 (t, 1H), 7.07-7.17 (m, 6H), 7.22-7.33 (m, 2H), 7.87 (t, 1H), 8.04 (brs, 2H), 8.61 (s, 1H)	505 $(MH)^+$
4		2.39-2.41 (m, 2H), 2.70-2.79 (m, 2H), 2.94-3.10 (m, 2H), 3.25-3.37 (m, 2H), 3.35-3.40 (m, 4H), 3.60-3.62 (m, 1H), 7.06-7.17 (m, 6H), 7.71 (d, 2H), 7.90 (t, 1H), 8.06 (brs, 2H), 8.54 (s, 1H)	538 $(MH)^+$

Intermediates for Example 2

[4-({[2-{[(3*R*)-3-Amino-4-(2-fluorophenyl)butanoyl]amino}-2,3-dihydro-1*H*-inden-2-yl)carbonyl]amino}methyl)phenyl]acetate

^{1}H NMR (DMSO): 2.35-2.41 (m, 2H), 2.70-2.80 (m, 1H), 2.90-2.97 (m, 1H), 3.08-3.23 (m, 2H), 3.35-3.60 (m, 5H), 4.20-4.24 (m,1H), 7.05-7.32 (m, 12H), 7.95 (brs, 2H), 8.30 (t, 1H), 8.57 (s, 1H); MS m/z 504 $(MH)^+$.

tert-Butyl {4-({[2-{[(3*R*)-3-[*tert*-butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoyl]amino}-2,3-dihydro-1*H*-inden-2-yl)carbonyl]amino}methyl)phenyl]acetate

^{1}H NMR (DMSO): 1.23 (s, 9H), 1.36 (s, 9H) 2.25 (d, 1H), 2.55-2.62 (m, 1H), 2.73-2.77 (m, 1H), 3.12-3.21 (m, 1H), 3.44-3.52 (m, 4H), 3.94-4.03 (m, 1H), 4.11-4.32 (m, 2H), 6.61 (d, 1H), 7.03-7.20 (m, 12H), 8.16 (t, 1H), 8.25 (s, 1H); MS m/z 682 (M+Na).

Intermediates for Example 3

2-{[(3*R*)-3-Amino-4-(2-fluorophenyl)butanoyl}amino}-*N*-{[(propylsulfonyl)amino]ethyl}indane-2-carboxamide

^{1}H NMR (DMSO): 0.95 (t, 3H), 1.60-1.70 (m, 2H), 2.41-2.43 (m, 2H), 2.77-2.84 (m, 1H), 2.90-2.95 (m, 5H), 3.07-3.17 (m, 4H), 3.38-3.48 (m, 2H), 3.60-3.66 (m, 1H), 6.95 (t, 1H), 7.07-7.17 (m, 6H), 7.22-7.33 (m, 2H), 7.87 (t, 1H), 8.04 (brs, 2H), 8.61 (s, 1H); MS m/z 505 $(MH)^+$.

Tert-butyl [(1*R*)-1-(2-fluorobenzyl)-3-oxo-3-[({2-[(propylsulfonyl)amino]ethyl}amino)carbonyl]-2,3-dihydro-1*H*-inden-2-yl}aminopropyl]carbamate

^{1}H NMR ($CDCl_3$): 0.94 (t, 3H), 1.25 (s, 9H), 1.59-1.67 (m, 2H), 2.23 (d, 2H), 2.59-2.62 (m, 1H), 2.72-2.76 (m, 1H), 2.89-2.94 (m, 4H), 3.10-3.14 (m, 4H), 3.41-3.50 (m, 2H), 3.94-3.97 (m, 1H), 6.58 (d, 1H), 6.88 (t, 1H), 7.01-7.21 (m, 8H), 7.71 (brs, 1H), 8.30 (s, 1H); MS m/z 627 (M+Na).

Intermediates for Example 4

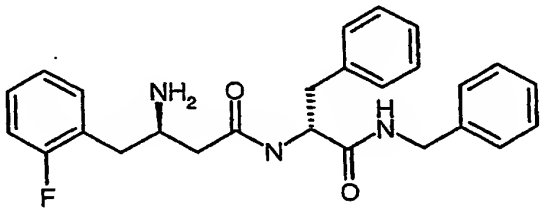
2-{[(3*R*)-3-Amino-4-(2-fluorophenyl)butanoyl]amino}-*N*-{2-[4-(aminosulfonyl)phenyl]ethyl}indane-2-carboxamide

^{1}H NMR (DMSO): 2.39-2.41 (m, 2H), 2.70-2.79 (m, 2H), 2.94-3.10 (m, 2H), 3.25-3.37 (m, 2H), 3.35-3.40 (m, 4H), 3.60-3.62 (m, 1H), 7.06-7.17 (m, 6H), 7.71 (d, 2H), 7.90 (t, 1H), 8.06 (brs, 2H), 8.54 (s, 1H); MS m/z 538 $(MH)^+$.

Tert-butyl [(1*R*)-3-({2-[({2-[4-(aminosulfonyl)phenyl]ethyl}amino)carbonyl]-2,3-dihydro-1*H*-inden-2-yl}amino)-1-(2-fluorobenzyl)-3-oxopropyl]carbamate

^{1}H NMR ($CDCl_3$): 1.23 (s, 9H), 2.22 (d, 2H), 2.59-2.63 (m, 1H), 2.71-2.76 (m, 3H), 3.03-3.10 (m, 2H), 3.32-3.47 (m, 4H), 3.96-4.00 (m, 1H), 6.61 (d, 1H), 7.04-7.17 (m, 8H), 7.24 (s, 1H), 7.33 (d, 2H), 7.69-7.72 (m, 3H), 8.19 (s, 1H); MS m/z 661 (M+Na).

Example 5: *N*-[(3*R*)-3-Amino-4-(2-fluorophenyl)butanoyl]-*N*-benzyl-D-phenylalaninamide hydrogen chloride salt.



To a stirred solution of (*R*)-3-*tert*-butoxycarbonylamino-4-(2-fluoro-phenyl)-butyric acid (2.00 g, 6.75 mmol) in DCM (100 mL) was added sequentially HOBt (1.10 g, 8.11 mmol), methyl D-phenylalaninate (1.46 g, 6.75 mmol), triethylamine (1.88 ml, 13.5 mmol) and EDCI (1.55 g, 8.11 mmol). The mixture was stirred at ambient temperature for 16 h. The reaction mixture was then washed sequentially with 2M HCl (50 ml), aqueous sodium bicarbonate (50 ml) and brine (100 ml). The organic phase was separated, dried with magnesium sulphate and concentrated under reduced pressure to leave a white gum. The residue was purified by flash silica gel chromatography (eluting with DCM to 10 % MeOH/DCM) to give *N*-[(3*R*)-3-amino-4-(2-fluorophenyl)butanoyl]-*N*-benzyl-D-phenylalaninamide (2.91 g, 94%) as a colourless solid. ^{1}H NMR ($CDCl_3$): 1.38 (s, 9H), 2.32 (dd, 1H), 2.42 (dd, 1H), 2.82-2.96 (m, 2H), 3.06 (dd, 1H), 3.14 (dd, 1H), 3.76 (s, 3H), 4.10 (m, 1H), 4.84 (m, 1H), 5.38 (brs, 1H), 6.02 (brd, 1H) and 6.94 –7.36 (m, 9H); MS m/z 481 (M+Na).

A solution of this material (2.90 g, 5.88 mmol) in THF (50 mL) and MeOH (3 ml) was treated with a solution of 2M aqueous sodium hydroxide (16.1 mL). The reaction mixture was allowed to stir at ambient temperature for 16 hours. The mixture was concentrated under reduced pressure and the aqueous residue was acidified to pH 2 with 2M HCl at which point a voluminous white precipitate formed, the precipitate was filtered off and washed with water and diethyl ether. The solid was dried *in vacuo* to give *N*-[(3*R*)-3-amino-4-(2-fluorophenyl)butanoyl]-D-phenylalanine as a colourless solid (0.241 g, 94%). ^{1}H NMR (DMSO): 1.23 (s, 9H); 2.18-2.35 (m, 2H), 2.44-2.62 (m, 2H), 2.87 (dd, 1H), 3.06 (dd, 1H), 3.96 (m, 1H), 4.46 (m, 1H), 6.55 (d, 1H), 7.00-7.30 (m, 9H), 8.22 (d, 1H); MS m/z 467 (M+Na).

To a solution of this acid (0.100g, 0.23 mmol) in DCM (5 mL) was added sequentially HOBt (0.037 g, 0.27 mmol), benzylamine (25 µL, 0.23 mmol), triethylamine (63 µL, 0.45 mmol) and EDCI (0.052 g, 0.27 mmol). The mixture was stirred at ambient temperature for 16 h. and

then washed sequentially with 2M HCl (2 X 10 ml), sat. aqueous sodium bicarbonate (10 ml) and water (10 ml). The organic phase was separated, dried with magnesium sulphate and concentrated under reduced pressure to give a colourless solid which was purified by flash silica gel chromatography eluting with (DCM to 10 % MeOH/DCM) to give *N*-benzyl-*N*-[(3*R*)-3-[(*tert*-butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoyl]-D-phenylalaninamide (0.106 g, 89%) as a colourless solid. ^{1}H NMR (DMSO): 1.22 (s, 9H), 2.18-2.35 (m, 2H), 2.44-2.62 (m, 2H + water), 2.80 (dd, 1H), 3.02 (dd, 1H), 3.92 (m, 1H), 4.06 (d, 2H), 4.60 (m, 1H), 6.57 (d, 1H), 7.00-7.30 (m, 14H), 8.14 (d, 1H), 8.40 (t, 1H)

4M HCl in dioxan was added to this solid (106 mg, 0.191 mmol) and the mixture was stirred for 16 hours. The solvent was evaporated under reduced pressure and the residue triturated with ether. The ether was evaporated to afford the title compound as a colourless solid (90 mg, 96%). ^{1}H NMR (DMSO): 2.20-2.40 (m, 2H), 2.60-2.78 (m, 2H), 2.84 (dd, 1H), 3.00 (dd, 1H), 3.50 (m, 1H), 4.18-4.30 (m, 2H), 4.56 (m, 1H), 7.05-7.38 (m, 14H), 7.94 (brs 2H), 8.44 (d, 1H), 8.58 (t, 1H); MS m/z 434 $(MH)^+$.

Examples 6 to 9

The following examples were synthesised in a similar way to Example 5 using the appropriate commercially available amines in place of benzylamine, but were isolated as the free bases using the following procedure:

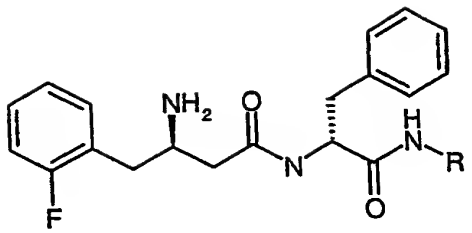
The hydrochloride salt was taken up in DCM (10 ml) and washed sequentially with 2M NaOH (2 X 20 ml) and water (20 ml) the organic layer was dried over $MgSO_4$ and the DCM was removed *in vacuo* to give the free bases as colourless solids.

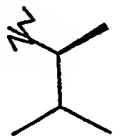
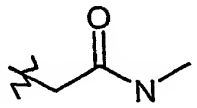
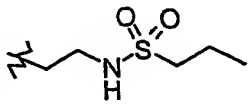
Example 6: *N*-[(3*R*)-3-Amino-4-(2-fluorophenyl)butanoyl]-*N*-methyl-D-phenylalaninamide

Example 7 *N*-[(3*R*)-3-Amino-4-(2-fluorophenyl)butanoyl]-*N*-[(1*S*)-1,2-dimethylpropyl]-D-phenylalaninamide

Example 8 *N*-[(3*R*)-3-Amino-4-(2-fluorophenyl)butanoyl]-D-phenylalanyl-N^1-methylglycinamide

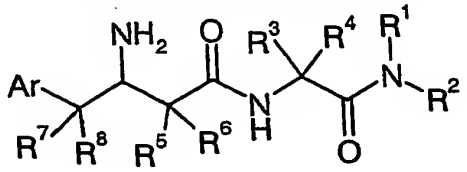
Example 9 *N*-[(3*R*)-3-Amino-4-(2-fluorophenyl)butanoyl]-*N*-benzyl-D-phenylalaninamide



Example	R	^{1}H NMR	MS m/z
6		2.19 (dd, 1H), 2.40 (dd, 1H), 2.62-2.82 (m, 5H), 3.0-3.16 (m, 2H), 3.40 (m, 1H), 4.64 ((apparent q, 1H), 6.60 (brs, 1H), 6.96-7.35 (9H, m), 7.64 (brd 1H)	358 $(MH)^+$
7		($CDCl_3$): 0.78 (d, 3H), 0.88 (d, 3H), 1.58 (1H + water), 2.12 (dd, 1H), 2.38 (dd, 1H), 2.62 (dd, 1H), 2.75 (dd, 1H), 3.03 (dd, 1H), 3.11 (dd, 1H), 3.34 (m, 1H), 3.73 (m, 1H), 4.58 (apparent q, 1H), 5.79 (brd, 1H), 6.98-7.32 (m, 9H), 7.77 (d, 1H)	414 $(MH)^+$
8		($CDCl_3$): 2.14 (dd, 1H), 2.39 (dd, 1H), 2.64 (dd, 1H), 2.66-2.80 (m, 4H), 3.02 (dd, 1H), 3.21 (dd, 1H), 3.26 (m, 1H), 3.75 (dd, 1H), 3.86 (dd, 1H), 4.60 (m, 1H), 6.72 (m, 1H), 6.90-7.32 (m, 9H), 7.65 (d, 1H), 7.95 (t, 1H)	415 $(MH)^+$
9		(DMSO): 0.96 (t, 3H), 1.64 (sex, 2H), 2.32 (dd, 1H), 2.40-3.30 (m 11H), 3.49 (m, 1H), 4.42 (m, 1H), 7.02-7.38 (m, 9 H), 8.11 (brs, 3H), 8.20 (t, 1H), 8.32 (d, 1H)	493 $(MH)^+$

Claims

1. A compound of formula (I) or a pharmaceutically-acceptable salt thereof,



(I)

wherein:

Ar is phenyl optionally substituted with 1, 2, 3, 4 or 5 groups independently selected from R^9;

R^9 is selected from halo, (1-6C)alkyl (optionally substituted with 1-5 halo), (1-6C)alkoxy (optionally substituted with 1-5 halo) and cyano;

R^1 is selected from hydrogen and (1-6C)alkyl;

R^2 is selected from hydrogen, (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylAR2, -(1-6C)alkyl(3-8C)cycloalkyl, -(1-6C)alkylHET1, -(1-6C)alkylHET2, -(1-6C)alkylCO_2(1-6C)alkyl, -(1-6C)alkylCO_2(3-8C)cycloalkyl, -(1-6C)alkylCO_2AR1, -(1-6C)alkylCO_2HET1, -(1-6C)alkylOCO(1-6C)alkyl, -(1-6C)alkylOCO(3-8C)cycloalkyl, -(1-6C)alkylOCOAR1, -(1-6C)alkylOCOHET1, -(1-6C)alkylCO(1-6C)alkyl, -(1-6C)alkylCO(3-8C)cycloalkyl, -(1-6C)alkylCOAR1, -(1-6C)alkylCOHET1, -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCO(3-8C)cycloalkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONH(3-8C)cycloalkyl, -(1-6C)alkylCON-di(1-6C)alkyl, -(1-6C)alkylCONHAR1, -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylN-di(1-6C)alkyl , -(1-6C)alkylNHAR1, -(1-6C)alkylNH(HET1), -(1-6C)alkylNHSO_2(1-6C)alkyl, -(1-6C)alkylSO_2NH(1-6C)alkyl, and -(1-6C)alkylSO_2N-di(1-6C)alkyl;

or

R^1 and R^2 may together form a (3-8C)cycloalkyl , (5-12C)bicycloalkyl, or (6-12C)tricycloalkyl ring, or a ring defined by HET1; wherein a ring comprising R^1 and R^2 is optionally substituted by 1 or 2 substituents independently selected from halo, (1-6C)alkyl, halo(1-6C)alkyl, (1-6C)alkoxy, cyano, carboxy, carboxy(1-6C)alkyl, –CO(1-6C)alkyl, –

CO_2(1-6C)alkyl, (1-6C)alkylamino, di-(1-6C)alkylamino, –NHCO(1-6C)alkyl, –CONH(1-6C)alkyl, -CONdi-(1-6C)alkyl and HET1;

R^3 and R^4 are independently selected from hydrogen, (1-6C)alkyl, -(1-6C)alkyl(3-8C)cycloalkyl, -(1-6C)alkyl(3-8C)cycloalkenyl, -(1-6C)alkylAR1, -(1-6C)alkylAR2, -(1-6C)alkylHET1, and -(1-6C)alkylHET2; or

R^3 and R^4 together form a ring as defined by (3-8C)cycloalkyl, AR2, HET1 or HET2;

R^5, R^6, R^7 and R^8 are independently selected from hydrogen and (1-6C)alkyl;

AR1 is optionally substituted phenyl;

AR2 is an optionally substituted 8-, 9- or 10-membered, unsaturated, partially or fully saturated bicyclic carbocylic ring;

HET1 is an optionally substituted 3-, 4-, 5- or 6-membered, unsaturated, partially or fully saturated monocyclic heterocyclyl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), linked via a ring carbon atom, or a ring nitrogen atom if the ring is not thereby quaternised, and wherein any available carbon, sulfur or nitrogen atom may be oxidised;

HET2 is an optionally substituted 8-, 9- or 10-membered, unsaturated, partially or fully saturated bicyclic heterocyclyl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and linked via a ring carbon atom in either of the rings comprising the bicyclic system;

wherein suitable optional substituents on AR1, AR2, HET1 and HET2 are 1, 2, 3, 4 or 5 substituents independently selected from halo, (1-6C)alkyl, halo(1-6C)alkyl, dihalo(1-6C)alkyl, trifluoromethyl, (1-6C)alkoxy, carboxy(1-6C)alkyl, carboxy(1-6C)alkoxy, hydroxy, amino, (1-6C)alkylamino, di(1-6C)alkylamino, -$CONH_2$, –CONH(1-6C)alkyl, -CONdi(1-6C)alkyl, –NHCO(1-6C)alkyl, -$S(O)_2NH_2$, –SO_2NH(1-6C)alkyl, -SO_2Ndi(1-6C)alkyl and –$NHSO_2$(1-6C)alkyl.

2. A compound of formula (I) as claimed in claim 1 and pharmaceutically-acceptable salts or in-vivo hydrolysable esters thereof for use as a medicament.

3. A compound of formula (I) as claimed in claim 1 or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof for use in a method of treatment of the human or animal body by therapy.

4. The use of a compound of formula (I) as claimed in claim 1, or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof in the manufacture of a medicament for use in the production of an inhibition of DPP-IV activity in a warm-blooded animal such as a human being.

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